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Background Paper


Environmental Tobacco Smoke: Properties, Measurement Techniques and Applications

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Environmental tobacco smoke (ETS) results from the mixing of two different sources (types) of tobacco smoke; that which emanates from the burning end of a cigarette (sidestream smoke (SS)) and that which is exhaled by the smoker (exhaled mainstream smoker (EMS)). As sidestream and exhaled mainstream smoke enter the environment, they are mixed and diluted to form ETS. The relative contributions of SS and EMS to the composition of ETS is not fixed but depends on both product typeⁱ (see Table 1) and the behavioural characteristics of the smoker.

Table 1 Estimated Contribution of Exhaled Mainstream Tobacco Smoke to the Concentration of ETS Constituents

Cigarette Type	Constituent		
	CO (%)	Particulate (%)	Nicotine (%)
		Phase	
Flue-cured	11	43	7
US-Blend	13	15	9
Filter Ventilated	3	20	1

There is little published information on the characteristics of EMS. By comparison, SS has been studied in depth in numerous publications over many years⁽¹⁾. Since the properties of ETS are largely determined by the characteristics of sidestream smoke, it is instructive to examine the composition and behaviour of this complex aerosol in a little more detail.

Composition based on Sidestream Studies

Prior to 1989, most studies of SS used a small closed water-cooled chamber for the generation and collection of SSⁱⁱ (Figure 1) which has been largely replaced by the British American Tobacco (BAT) 'fish-tailed' chamber pictured below (see Figure 2)ⁱⁱⁱ. Cigarettes are placed, lit and smoked at the base of the fishtail. Sidestream constituents are collected by drawing air at the rate of from 2 to 3 litres per minute over the burning cigarette and through an appropriate trapping or collection medium. These are a Cambridge® filter holder and pad for particulates followed by impingers and trapping solutions for gas phase constituents. Analytical techniques for specific compounds are similar to those used for mainstream smoke (see reference ^{iv} for example).

In 1998 the Government of Canada introduced a reporting requirement for sidestream emissions and mandated the specific methodologies to be employed. This expanded reporting requirement includes 42 compounds in 8 chemical classes for all tobacco products which are burnt under normal conditions of use (i.e. cigarettes, cigars, leaf tobacco, roll-your-own tobaccos, cigars, pipe tobaccos, bidis and kreteks)^v. Since ETS is due, largely, to the sidestream smoke which emanates from the lit end of cigarettes, large reductions in ETS might be possible if sidestream emissions were reduced. Implicit in this requirement is the recognition that Canadians will continue to smoke in private areas, such as the home, in spite of total bans in many public places^{vi}.

Tables 4.3-1 and 4.5.4-1 which may be found in reference ^{vii} contain levels for many toxic constituents found in both the mainstream and sidestream tobacco smoke from a reference (control) cigarette. The results illustrate a number of points.

Sidestream and mainstream smoke are similar in terms of chemical composition but differ with respect to the concentration of specific components.

Sidestream yields (SS) are considerably greater than mainstream yields (MS)

It is also worth noting that although mainstream yields increase dramatically under 'intense' smoking conditions, the corresponding sidestream yields actually decrease^{viii}. Consequently sidestream yields under 'standard' smoking conditions represent the maximum potential contribution of sidestream smoke to ETS.

⁽¹⁾ See Klus, H., and Kuhn, Distribution of various tobacco smoke components among mainstream and sidestream smoke. Beitrage Tabakforschung Internatl. 1982; 11:229-265 (137 references) for a summary of results from early studies. Consult Klus, H, Distribution of Mainstream and Sidestream Cigarette Smoke Components. Rec. Adv. Tob. Sci. 1990; 16:189-232 for a more recent review (90 references)

Sidestream and mainstream yields are both related to “tar” yield but there are significant differences in the nature of the dependency. This point can be demonstrated using the results from a 40 brand survey of yields of the carcinogen, benzene⁽²⁾. Whereas mainstream benzene yields *increase* with increasing “tar”, sidestream yields decrease (i.e. low yield “tar” brands deliver more benzene to the environment than do high yield brands). This is also true of the carcinogenic benzo[a]pyrene as shown in figure 3B.

Properties of ETS

The properties of ETS can not be explained on the basis of the chemical composition of either exhaled mainstream smoke or sidestream smoke. ETS is a dynamic mixture of both and is continually changing due to chemical and photochemical reactions, adsorption and absorption onto surfaces and reaction with the various components in ventilation systems. This point can be illustrated by examining changes in the carbonyl composition of ETS as it ‘ages’ under controlled laboratory conditions⁽³⁾.

In this project cigarette smoke was generated by the sequential smoking of single cigarettes in a 27m³ controlled environment room. Temperature was maintained at 22°C, relative humidity at 40% with a ventilation rate of 0.4 air exchanges per hour (ACH). Samples were acquired every 20 minutes and the carbonyl content determined^{ix}. As expected, reactive compounds, such as formaldehyde, decrease relative to other compounds such as acetaldehyde which increases. There is also a relative increase in acrolein with time which may help explain the eye irritation experienced by many in the presence of ETS.

Differences in reactivities have implications for any procedure that purports to ‘measure’ ETS. For example, it has been reported that nicotine in ambient air decays 3.8 times as fast as tobacco smoke particulates; this point is crucial to the question of estimating ETS exposures based on nicotine^x. The potential magnitude and direction of potential errors can be determined through simulations using models developed for this purpose^{xi}. Figure 5 illustrates the results for both ETS particulates and environmental nicotine in the air of a typical 340 m³ home where the effective ventilation rate is 0.75 ACH^x. In developing the simulation it was assumed that cigarette emissions were known^{viii} and equivalent to the continuous smoking of one cigarette.

In this simulation, equilibrium values for nicotine (19 ug/m³) are reached within approximately 2.5 hours but over 4 hours of smoking are required before ETS particulates reach the limiting value of about 300 ug/m³. Thus the particulate (P):nicotine (N) ratio undergoes continual change from an initial value of about 8 to a final value of about 15. Using the average P/N value of 13.6 clearly overestimates ETS particulates initially but later, results in overestimate. Consequently, it is extremely important to ensure adequate sampling times when estimating the concentration of one or more constituents of ETS based on the concentration of another^{xii}.

Estimation of ETS Exposure

Several types of environmental tobacco smoke (ETS) exposure measures have been used, including: questionnaires to record spousal smoking habits; questionnaires to record exposures at home and outside the home; biological sampling using tobacco smoke markers such as thiocyanate, carbon monoxide, carboxyhemoglobin, and nicotine; stationary air sampling to measure carbon monoxide, aromatic hydrocarbons, respirable suspended particulates, and nicotine; personal sampling with pump-driven nicotine and respirable suspended particulate samplers; and personal sampling with a diffusion-based nicotine monitor. Biological markers, such as salivary, urinary, or blood cotinine can be used to determine a person's recent exposure to nicotine. Biological markers, such as thiocyanate and carbon monoxide are not specific for environmental tobacco smoke^{xiii}.

Exposures to ETS consist of contact between individuals and ETS air contaminants at specific concentrations for a specified time period. ETS exposures are therefore expressed as concentration multiplied by time. It is crucial that the exposure data be gathered on a time frame related to the health or comfort effect of concern. Studies of ETS-associated diseases (e.g. lung cancer) require ETS exposure measures integrated over periods of years, whereas studies of ETS-associated acute effects (e.g. odour,

² Contract research project sponsored by Health Canada. Reference: Rickert, W.S., Tobacco Smoke Benzene and Phenols: Results from a 40 Brand Survey of Canadian Cigarettes. Report dated April 24, 1992, Canadian Office of Tobacco Control (Contract No. H4078-1-C052/01-SS)

³ Contract research project sponsored by Health Canada. Reference: Rickert, W.S., Evaluation of the Potential Contribution of Tobacco Smoke to Levels of Ambient Air Pollutants. Report dated April 30, 1993. Canadian Office of Tobacco Control (Contract No. H4078-2-C511/01-SS)

eye irritation) require exposure measures over a period of minutes. Specification of the biological response time under study is important in developing an ETS exposure assessment strategy.

Direct and indirect techniques can be utilized which permit an accurate assessment of an individual's or a population's exposure to ETS. The direct method of ETS exposure can be assessed through the use of personal monitoring and biomarkers, whereas the indirect method models exposures through the use of air-sampling, space measurements, and questionnaires. Personal monitors can be used to estimate ETS air contaminant concentrations at or near the breathing zone and are worn by an individual as he or she conducts their daily activities^{xiv}. Air monitoring of environmental tobacco smoke constituents provides a more direct estimate of room concentration, or, if the monitor is worn by the subject, of personal exposure. Vapour phase nicotine, which is a specific marker of ETS exposure, can be measured with either active or passive samplers^{xv}. Active samplers use a pump to pull airborne contaminants through a collection device, while passive samplers depend on molecular diffusion to deliver the contaminant to the collection medium. Thus they provide an integrated measure of exposure^{xiv}. Biomarkers for ETS are actually indicators of dose. It is, however, difficult to relate biomarker levels to specific air exposures because of limitations in the understanding of such factors as uptake, distribution, metabolism, and site and mode of action of the contaminants. The indirect method of assessing ETS exposures utilizes air-sampling measurements of ETS contaminants in spaces, modeling, and questionnaires to estimate ETS concentrations in indoor environments. These measured or modeled concentrations are then combined with estimates or measurements of an individual's time in those environments to calculate exposure^{xvi}.

Area Monitoring

Rationale

Although epidemiology has demonstrated that ETS exposure is associated with increased risk, this type of study may not be able to answer more specific questions concerning ETS and human health^{xvii}. For example, epidemiological investigations have not attempted to identify or to quantify the carcinogens, mutagens, and other types of toxicants found in ETS. This is due to the fact that ETS has a range of compositions, depending on ventilation, surfaces, source input rates, lighting, and other factors which depend on the specific environment under consideration^{xviii}. Given the complex unstable nature of ETS it can not be "measured" in the classical sense. The best that can be hoped for is an assessment of specific constituents of known significance with respect to human health or the measurement of constituents related, in some predictable manner, to one or more tobacco smoke toxins.

Use of Surrogates

Under equilibrium conditions, it is possible to infer the concentration of ETS based on a few key indicators or surrogates. Ideally, surrogates should have the following properties^{xix} unique or nearly unique to the tobacco smoke so that other sources are minor in comparison. present in sufficient quantity such that it can be easily detected in air, even at low smoking rates similar in emission rates for a variety of tobacco products in a fairly consistent ratio to the individual contaminant of interest or category of contaminants of interest (e.g., suspended particulates) under a range of environmental conditions encountered and for a variety of tobacco products.

No single measure has met all the criteria outlined above, nor has any measure been universally accepted or recognized as predictive of ETS concentration and potential exposure and dose. Nicotine, carbon monoxide, 3-ethenylpyridine, nitrogen dioxide, pyridine, aldehydes, nitrous acid, acrolein, benzene, toluene, myosmine, and several other compounds have been used or been suggested for use as markers or proxies for the vapour-phase constituents of ETS. Tobacco-specific nitrosamines, particle-phase nicotine and cotinine, solanesol, polonium-210, benzo[a]pyrene, potassium, chromium, and respirable suspended particle (RSP) mass are among the air contaminants used or suggested for use as markers for particle-phase constituents of ETS^{xx}. This list has been reduced considerably in recent studies to five ETS constituents (see references^{xiv,xxi,xxii}). These are respirable suspended particulates, ultraviolet and/or fluorescent particulate matter, and solanesol for ETS particulate phase and nicotine and 3 vinyl pyridine for the gas phase. Each is described in more detail in the following sections.

Respirable Suspended Particulates (RSP)

The combustion of tobacco results in the emission of significant quantities of RSP in the indoor environment, amounts which result in measurable RSP increases over background levels even under conditions of high ventilation and low smoking rates. Indoor RSP background levels emanate from both outdoor and indoor sources, other than ETS, and are chemically and biologically different from ETS-

associated RSP. A number of accepted methods, including gravimetric, optical, piezoelectric, etc., are used to measure personal RSP exposures and concentrations in indoor environments^{xxiii}.

In the gravimetric procedure, air is drawn at 2.0 l/min. through a 3.5 μ m cut-off impactor and particulates collected on a 1.0 μ m pore size membrane filter. The difference between the tare weight of the filter and the final weight after sampling is recorded as the mass of RSP^{xxiv}.

The reasons for using RSP as an environmental tobacco smoke marker include the following: (1) some of the most toxic compounds (including carcinogens) are found in the particle phase of ETS;(2) RSP concentrations can be correlated with number of cigarettes smoked in indoor environments; and (3) RSP is easily measurable above background levels in indoor environments as long as there are no other major sources of particles.

There are several disadvantages in the use of this tracer, however. RSP is not unique to environmental tobacco smoke, and it is not an adequate measure of environmental tobacco smoke exposure in the presence of other sources of RSP. For example, using a more specific marker for ETS particulates (UV-PM, see below) it has been demonstrated that only 10% of the total RSP was actually due to smoking^{xxv}.

Ultraviolet Absorbing Particulates (UV-PM)

A method has been described for rapid determination of tobacco smoke particulates was first published in 1990^{xxvi} and later developed as a standard (ASTM) method^{xxiv}. In this procedure, samples are drawn at 2.0 l/min through a 3.5 μ m cut-off impactor and collected on a 1.0 μ m pore size membrane filter. After weighing, the filters are extracted with methanol and the UV absorbance of the extract measured at 325 nm resulting in a value referred to as UV-PM.

In addition to simplicity, this method has a number of important advantages over traditional surrogate methods. UV-PM is a direct rather than indirect estimate of ETS concentration and is capable of quantitating particulates from tobacco smoke in the presence of particulates from other sources^{xxvii}.

This procedure has been evaluated in relation to other direct measures and has been found to be equivalent to traditional gravimetric methods UV-PM has been used to evaluate ETS concentrations in field settings^{xxv,xxviii}.

Nicotine

Passive^{xiii} and active^{xxix} ambient air monitoring continue to be widely used in assessments of ETS concentrations. The ASTM standard method involves collection by means of active sampling through XAD-4 resin and gas chromatographic analysis using a nitrogen selective detector. Limits of detection and quantitation have been reported to be 0.02 μ g/m³ and 0.2 μ g/m³ for an 8 h sample (sampling rate of 1L/min)^{xxx}

Nicotine is used as a tracer because it is unique to tobacco smoke and it is easily measurable at realistic concentrations in indoor environments. Potential disadvantages of nicotine as a tracer of environmental tobacco smoke include the following: (1) nicotine deposited on surfaces can be remitted to the gas phase, (2) only preliminary data are available on the removal of nicotine relative to other environmental tobacco smoke compounds in the indoor environment (3) there may be problems associated with the unambiguous sampling of gas- and particulate-phase nicotine and (4), it is not clear what ratio should be used in the conversion to μ g/m³ particulate matter (PM) (⁴.)

3-Vinylpyridine

3-Vinylpyridine is formed from nicotine during the smoking of tobacco products. Consequently it is found in mainstream and sidestream smoke of cigarettes and cigars and in environmental tobacco smoke. This compound has a major advantage over nicotine as a marker for the gas phase of ETS since studies from indoor environments indicate that gas phase nicotine is removed at a much faster rate than 3-vinylpyridine^{xxxi}. Since deposition losses of 3-vinylpyridine and *particulate phase nicotine* are very similar in indoor environments, vinylpyridine/particulate ratios would be expected to be less variable than the corresponding nicotine/particulate ratios^{xxxii}. Note that experiments conducted in indoor environments indicate that the observed ratio of particles to nicotine present in environments dominated by smoking vary from 6 to 50 g particles/g nicotine^{xxxii xxxiii xxxiv}.

⁴ It should be noted that the issue of the ratio of nicotine to PM is not critical since results for nicotine should not be used to estimate levels of PM. Nicotine is a gas phase component and has merit only within this context.

3-vinylpyridine can be determined in samples collected for nicotine^{xxxv} but levels will be less than those recorded for nicotine reducing its sensitivity as a marker^{xxxii}. ASTM has published a standard method for the determination of both compounds. This test method is based upon the collection of 3-vinyl pyridine by adsorption on XAD-4 resin, extraction of the resin and quantitation by gas chromatography. Limits of detection and quantitation have been determined to be 0.01 ug/m³ and 0.02 ug/m³ respectively (sampling rate of 1L/min for 8 h)^{xxxvi}. Average 3-vinylpyridine concentration over a 70 minute period after the smoking of four IRI Kentucky reference cigarettes (30m³ room) was 738 nmol/m³; the corresponding values for nicotine were: gas phase 3800 nmol/m³ and particulate phase 153 nmol/m³^{xxxv}.

Solanesol

Solanesol, a trisesquiterpenoid alcohol characteristic of the Solanaceae family of plants which includes tobacco, has also been used as a marker for ETS particulate matter^{xxxvii}. Like nicotine, it is anticipated that the only measurable contribution of solanesol to an indoor environment would be from tobacco sources. Solanesol is, of course, characteristic of plants in the Solanaceae family, a member of which is the Nicotiana genus. Many other members of this family that contain solanesol are also those that contain traces of nicotine, e.g., tomato, potato, eggplant, and pepper. Outside of a remote possibility arising from cooking sources, the potential for interference is extremely minute.

Unlike nicotine, solanesol is not expected to shift equilibrium between vapour and particle phases of the ETS aerosol under any normal conditions encountered in an indoor environment. Additionally, because of its high molecular weight and extreme nonvolatility, solanesol is truly associated only with the particle phase of ETS and will not be lost from filter pads used for collection due to evaporation (as can happen with nicotine, neophytadiene, and other major tobacco smoke constituents). This has been verified in chamber experiments using various combinations of filter pads and XAD-4 sorbet tubes connected in series^{xxxviii}. Solanesol is determined by extracting ETS-RSP filters^{xxiv} with methanol and then subjecting an aliquot to liquid chromatography. Limit of and detection has been reported to be 0.05 ug/m³^{xxxix}. In another set of experiments the average ratio of RSP to solanesol was determined to be 43^{xl}. Other Surrogates (+)-a-Tochopherol is found in whole tobacco, and tobacco smoke particulates leading to the suggestion that (+)-a-tochopherol could function as an ETS particulate marker^{xli}. Initial experiments have established that (+)-a-tochopherol to be equivalent to solanesol in terms of a consistent ratio to ETS-RSP's. However limits of detection were less than those established for solanesol-RSP (5 ug/m³ ETS-RSP vs. 0.4 ug/m³ respectively)^{xlii}

A commonly used system of color notation, developed by A.H. Munsell, uniquely identifies color in terms of three attributes; Hue (H), which is a circular 100 step scale describing a color position in the red..green..red-purple continuum; Value (V) or Lightness (L) which specifies the degree of grayness on a 10 point scale and Chroma (C) which, for a specific value of H, quantitates the degree of departure from neutral gray. Specific values for each of the attributes can be determined by reflectance spectrometry in which the light reflected from a xenon source is analyzed by a 20 channel photodiode array.

Tobacco smoke particulates have a characteristic colour which can be used as a tool for quantitation based on the Munsell system. In this procedure, ETS particulates are collected on fluorapore membranes as described for UVPM^{xxiv} and solanesol. Calibration curves of ETS-RSP and Hue (defined above) are linear with a lower detection limit of about 50 ug/m³. Although the method has the advantage of being non destructive, its lack of sensitivity severely limits its scope of application^{xliii}.

Surrogate Evaluation (A Home Environment Source Apportionment Study)

In 1994 a series of Canadian Government sponsored experiments⁽⁵⁾ was carried out to determine the ability of commonly used surrogates to correctly apportion ETS related constituents among common sources found in homes. These included cigarette smoke, oil-burning lamps, wood smoke, incense and candles. Experiments were carried out in a 37m³ controlled environment room with 0.5 air exchanges per hour; the median value recorded in a U.S. survey of 312 homes^{xvii} and was the ventilation rated employed in all experiments. Temperature was controlled at 21°C and the humidity at 40%. A brief description of pollutant sources is as follows:

⁵ Contract research project sponsored by Health Canada. Reference: Rickert, W.S., Validation of Methods for the Quantitation of ETS Constituents, Final Report dated June 30, 1994, Canadian Office of Tobacco Control (Contract File No. 066SS.H4078-3-C000)

Cigarettes (CSS and CSM)

ETS was produced by smoking a popular Canadian cigarette at a rate of 2 cigarettes per hour. This level was chosen as being that anticipated in the home environment for a one-pack-a-day smoker, who consumes 30% of his cigarettes at home during a 4 hour interval. It has been reported that ETS particulates from flue-cured tobacco, which is typical of Canadian cigarettes, are made up of 43% exhaled mainstream smoke (see Table 1). Consequently 2 types of cigarette smoke were employed; sidestream only (CSS) and sidestream plus 50% mainstream (CSM). A value of 50% was chosen as being easy to achieve and as representing a "worst case" scenario. Cigarettes were smoked sequentially by a Phipps and Bird single port smoking machine located in the centre of the room. Cigarettes were lit and replaced in sequential fashion without entering the room or disturbing the room environment. Since it took approximately 10 minutes to complete the smoking process, a typical hour consisted of 20 minutes no smoking followed by a 10 minute smoking period then another 20 minute non smoking period followed by a 10 minute smoking period with the cycle repeating for a total of 6 hours. Cigarettes were smoked according to standard protocols (puff volume, 35 ml; puff duration, 2 seconds and interpuff interval, 58 seconds).

Incense (INC)

Incense described as "Earth Scents - Rose" is a hand made 'natural' Canadian product. Segments of incense were approximately 140-180 mm long, about 3 mm in diameter, and weigh about 1.00 g on average. Between 6 and 8 were burnt during the 6 hour course of the experiment.

Candles (CAN)

White 12" taper candles were purchased under the brand name "Bayonette". Each candle was about 2 cm at the base (widest portion) and from 8-9" were burnt before replacement. Total candle weight was about 70 g and that 3 were consumed during the course of a 6 hour experiment. All three were burnt simultaneously not sequentially.

Lamp (LAP)

A common wick-type coal-oil burning lamp was used as a continuous source of emissions throughout the experiment.

Wood (WOD)

Hagen White Natural Cedar Shavings (no preservatives or additives) were ground in a Moulinex blender to the consistency of saw dust. 450 mg of this blend were used to fill Export A KSF filter tubes. The tubes were filled using a funnel made from a plastic disposable pipette. The ends of the cigarette tubes were then folded to prevent wood loss due to handling. Wood 'cigarettes' were continuously smoked on the Borgwaldt single port smoking machine with a 35 ml puff volume and 120 second puff interval. Pulverised wood 'Cigarettes' typically lasted for 5 puffs at these conditions. Both mainstream and sidestream smoke were allowed to diffuse freely into the room air.

Tobacco cigarettes were smoked separately and in conjunction with continuous a background from either an oil-lamp, incense, wood smoke or candles as summarized below.

- (1) Sidestream only (CSS)
- (2) Sidestream + 50% mainstream (CSM)
- (3) Candles (CAN)
- (4) Incense (INC)
- (5) Wood "cigarettes"(WOD)
- (6) Lamp (LAP)
- (7) (CSS) + (CAN)
- (8) (CSS) + (INC)
- (9) (CSS) + (WOD)
- (10) (CSS) + (LAP)
- (11) (CSM) + (CAN)
- (12) (CSM) + (INC)
- (13) (CSM) + (WOD)
- (14) (CSM) + (LAP)

Response variables which were measured included total and diffusion monitor nicotine, 3-vinylpyridine, oxides of nitrogen, carbon monoxide, HCN, respirable particulates (continuous and gravimetric), benzo[a]pyrene, 8 carbonyls, 6 phenolics, benzene, toluene, solanesol, and UV-PM.

Results

Both wood smoke and tobacco smoke produce particulates which absorb in the ultraviolet (UV-PM) as illustrated in Figure 6A. As a result, a regression of UV-PM on *total particulates* was found to be highly significant passing through the origin with a slope of 0.705 ($R^2=86.6\%$). The regression of solanesol on *total particulates* was not significant but with an intercept of $1.509 \mu\text{g}/\text{m}^3$ which is the average level of solanesol taken over all experiments. When tobacco smoke particulates (TSP) are considered, both solanesol and passive monitor nicotine "correctly" predicted the concentration of TSP in the presence of the strongest source of particulates, wood smoke.

The most significant source of the carcinogen benzene was burning incense. Burning candles and lamp oil contributed little if any benzene (95% confidence interval covers zero) while the most intense source of tobacco (CSM) resulted in levels of benzene which were only 21% of those found when burning incense was the only source of combustion. A similar pattern was found with respect to the relative contributions of various pollutant sources to levels of benzo[a]pyrene, another well known carcinogen (Figure 6B)

The following is summary of results for other common pollutants of indoor air

Source	Relative Ranking
Wood Smoke	highest for particulates highest for formaldehyde highest for acrolein highest for CO
Incense	highest for crotonaldehyde highest for benzo[a]pyrene highest for benzene/toluene
Tobacco Smoke	highest for hydrogen cyanide highest for propanaldehyde highest for acetaldehyde
Candles	highest for NO

Three "best" candidates for ETS surrogates based on prediction ability for particulates unique to ETS in the presence of other particulates were nicotine and solanesol. Since UV-PM is produced, to a major extent, by sources other than tobacco, *it should be used with caution*. Since solanesol is more difficult and, therefore, costly to determine, it would seem reasonable to use passive monitor nicotine as the single best choice as a tobacco smoke surrogate. However, this ignores three major considerations.

Since nicotine is revolatilized from surfaces, concentrations in ambient air reflect the sum of past and current smoking. Consequently, it is possible to obtain measurements for nicotine in environments where smoking has not taken place for some time. Since nicotine is ubiquitous in the environment, contamination of samples taken for analysis is always an important consideration. Nicotine is not found in the particulate phase in ETS; consequently it is not an adequate indicator for tobacco smoke particulates. Solanesol is found only in the particulate phase and a reasonable surrogate for tobacco smoke particulates. Consequently, when resources permit, it is recommended that *both solanesol and nicotine* be used to estimate levels of ETS.

Biomonitoring

Nicotine, Cotinine and Trans 3-hydroxy Cotinine in Biological Fluids

After absorption and biotransformation of nicotine, the urinary distribution of nicotine phase I metabolites is : nicotine 10%, cotinine 13%, trans-3'-hydroxycotinine 35%, nicotine-N'-oxide 7%, cotinine-N'-oxide 4% and demethylcotinine 2%; phase II metabolites include nicotine glucuronide 3%, cotinine glucuronide 17% and trans-3'-hydroxycotinine glucuronide 9%^{xliv}. Cotinine is commonly used as a biomarker for exposure to ETS. However, large interindividual variations exist in the biodisposition of cotinine^{xlv,xlvi,xlvii,xlviii,xlix}. Moreover, this metabolite would be a relevant biomarker of ETS exposure only if it is one of the major end-metabolites of the parent compound. This is not the case^{i,ii,iii} and puts into question the use of cotinine as a biomarker at low levels of exposure. *At the very least, studies need to be done to compare both cotinine and 3'-hydroxycotinine as potential markers for exposure to nicotine.*

Another question which needs to be addressed is the ratio of nicotine (and its metabolites) to other tobacco smoke constituents, including polycyclic aromatic hydrocarbons, nitrosamines etc. Mainstream

Smoke (that inhaled by the smoker) is different from the EMS and SS which comprise ETS^{liv,lv}. As a consequence of these differences, *estimates of ETS exposure based on measures of nicotine or its metabolites in biological fluids of nonsmokers is likely to be misleading, at least in terms of increased lung cancer incidence*. An ETS-exposed person, even though excreting the same amount of urinary cotinine, may have been exposed to 10 times less RSP than MS-exposed smokers^{lvi}.

The general conclusions of many ETS studies that measure nicotine and/or cotinine are: (1) that experimental data are not always comparable among different studies, in particular with regard to urinary excretion; (2) because of its longer half-life, cotinine is likely to be a more suitable marker than nicotine; (3) saliva and urinary concentrations of cotinine correlate with serum concentrations; (4) passive smokers have, in their physiological fluids, concentrations of cotinine equivalent to a few ng/ml or ng/mg creatinine as compared to hundreds or thousands of ng/ml or ng/mg creatinine in active smokers; (5) such parameters might be valid for estimating acute exposure to relatively high levels of ETS; and (6) at low levels of exposure to ETS, nonsmokers have concentrations of nicotine and/or cotinine in their biological fluids, which are not very different from those measured in nonsmokers not exposed to any identified ETS^{xliv}. However, cotinine is the best available biomarker of ETS exposure at present^{lvii}.

Molecular Level Markers

Biomarkers for ETS-related Carcinogens

Among the carcinogens found in tobacco smoke are benzene, volatile and tobacco-specific N-nitrosamines (TSNA), aromatic amines, polynuclear aromatic compounds and polonium-210^{lviii}. Undiluted sidestream smoke contains higher concentrations of certain carcinogens than mainstream smoke, including benzo(a)pyrene (BP) (2.5- to 3.5- fold) and 4-aminobiphenyl (31-fold). These carcinogens have been identified using analytical methods for the detection of carcinogen metabolites or their adducts to proteins. Carcinogen biomarkers such as these promise to be important in delineating the role of ETS as a possible cause of lung cancer in nonsmokers. The incorporation of biomarkers into epidemiological studies can potentially provide greater specificity in linking exposure and disease than conventional techniques. This approach has become known as "molecular epidemiology"^{lix}. There are now data in the literature on the uptake and metabolism by nonsmokers exposed to ETS of all three major classes of carcinogens in tobacco smoke: PAH, nitrosamines, and aromatic amines^{lx}.

The potential role of carcinogen biomarkers in helping to define relationships between cigarette smoke exposure and cancer may best be seen by considering their use in studies of active cigarette smoking and cancer. Cigarette smoking is recognized as the major cause of lung cancer worldwide, with relative risks typically 10 - 20 times greater in smokers than in nonsmokers. This has been documented through case-control and prospective epidemiological studies^{lxvii}. The relative risk for lung cancer and other cancers in smokers is so great that the application of carcinogen biomarkers has not been necessary to establish a potential causal relationship. Nevertheless, numerous carcinogen biomarker studies have been carried out. Examples include the quantitation of carcinogen hemoglobin adducts, carcinogen DNA adducts, and carcinogen metabolites in urine^{lxi}. These studies, which are generally small in scale and have been described as transitional epidemiological studies,^{lxiii} have bolstered the connection between smoking and cancer by providing a mechanistic framework for understanding it. At the same time, these studies have helped to validate carcinogen biomarkers through comparisons of their levels in smokers, who have documented exposure to carcinogens, with those of nonsmokers.

Carcinogen biomarkers can be used to strengthen the epidemiological findings. The ideal biomarker, which could integrate tobacco-specific carcinogen exposure and metabolic activation over a lifetime and provide an estimate of total internal dose of ETS, does not exist. At present, substitutes have to be used. Among the most common carcinogen biomarkers used are PAH-albumin adducts, and adducts related to aromatic amine including 4-aminobiphenyl (ABP), and N-nitrosamine exposure.

PAH-Albumin Adducts

A 1994 study^{lxiii} evaluated a number of complementary biomarkers in Hispanic and African-American preschool children and their mothers with varying exposure to ETS. The biomarkers used included serum cotinine and polycyclic aromatic hydrocarbon (PAH)-albumin adducts; PAH-albumin has a considerably longer half-life than cotinine (21 days).

The results demonstrated that ETS exposure of young children via their mothers' smoking is associated with increases in the internal dose of ETS (cotinine) and in the biologically effective dose of the PAH components of ETS (PAH-albumin adducts). Because of the observed correlation between protein and

DNA binding by PAH and other carcinogens, albumin adducts indicate that DNA damage is occurring. Thus, PAH-protein adducts provide dosimetry data that are relevant to potential risk of cancer from these carcinogens^{lxiv, lxv}. In this study, ETS was the most important environmental contributor to PAH-albumin adducts in nonsmokers. Maternal smoking was the greatest contributor to these biologic markers in the children. Another result of note was that levels of both cotinine and PAH-albumin adducts were markedly elevated in the mothers who smoked compared with the nonsmokers, with a significant correlation between cotinine and cigarettes per day. In the nonsmoking women, total passive smoking in the home was highly correlated with cotinine but not with albumin adducts, likely due to differences in the half-lives of the biomarkers^{lx}.

Aromatic Amines

In contrast to cancers of the upper respiratory tract, for which tobacco-specific N-nitrosamines (including NNK and NNAL), polynuclear aromatic compounds and radioisotopes have been implicated as causative agents, bladder cancer seems more likely to be caused by aromatic amines. Several studies have demonstrated proportionality between carcinogen binding to DNA and carcinogen binding to hemoglobin^{lxvi, lxvii}. Therefore, 4-aminobiphenyl hemoglobin adduct level has been used as a dosimeter for DNA damage in tissues of adult smokers.

Epidemiological studies and assessments of cancer risk from ETS have been limited by inadequate data on individual exposure to ETS and on the range of variability in human biologic response to that exposure. In particular, potential risks of ETS exposure to minorities, to young children and to women of reproductive age have not been well characterized. Biomarkers can be useful in addressing these gaps in knowledge by providing direct measurements of the internal and biologically effective dose of ETS, molecular effects, and susceptibility factors that modulate them.

Biological Variability

In a 1993 study^{lxviii} three different methods of estimating exposure, questionnaire, urinary cotinine and ambient nicotine, were compared on a cross-sectional basis in a population with varying degrees of exposure. Urinary cotinine and ambient nicotine concentrations were highly correlated with each other. This correlation suggests that, even though one is a measure of exposure and the other a measure of dose, they provide equally valid but redundant information about exposure in this study population. The choice between the two then depends on feasibility, and one component of feasibility is the variability of the measure; the greater variability the greater the number of measurements which must be made for accurate exposure estimation. While both measurements showed variability over time, urine cotinine was more variable. At least two factors contribute to this variability: the half-life of cotinine and the measurement of creatinine. Since the half-life of cotinine is 32-82 hours in young children, the level of cotinine in the urine is highly influenced by exposures over the past several days. Thus, this component of the variability reflects the true variability in the exposure. Standardizing urinary cotinine by creatinine introduces another potential source of variability, this one due to error. Examination of cases with unusually elevated cotinine:creatinine ratios found that the creatinine concentrations were very low. At low concentrations, very small laboratory measurement error has a large effect on the cotinine:creatinine ratio. Nonetheless, a stronger correlation was found between activity room nicotine and the cotinine:creatinine ratio than between nicotine and unstandardized cotinine, confirming the importance of adjusting for urine dilution^{lxviii}.

ETS in the Home Environment

There have been a number of recent studies of ETS exposure of adults living in major European cities^{lxix, lxx, lxxi, lxxii}. Exposure to ETS was estimated by direct measurement of RSP, surrogate measures (i.e. nicotine, 3-vinyl pyridine, UVPM, FLPM, solanesol) and biomonitoring (i.e. salivary cotinine). With respect to the home environment, exposure to nicotine and ETS particulates was reported to be 4 and 7 times more (respectively) than those obtained from the workplace. This conclusion was based on a sample set of 188 subjects who wore personal monitors for a 24 hour period^{lxxi}. Using cigarette equivalents as a measure (CE)^{lxxiii}, Phillips *et. al.* reported that housewives living with smokers could inhale up to 11 CE per annum based on the upper decile levels of exposure^{lxxii}. While the subject selection process does allow for some generalization, all of the data reported in these studies come from a single 24 hour period in the life of the subjects and from personal monitoring only. There are very few examples of studies that have attempted to assess ETS exposure in the home environment over an extended period of time. In one, reported Coultas *et. al.*^{lxxiv} four ETS markers were used to study ETS exposure in 10 homes on 10 sampling days: every other day on 10 sampling days, every other day over 10 days, and then 1 day every other week over 10 weeks. The mean concentrations of RSP in the 10 homes

ranged from 32.4 to 76.9 ug/m³ and concentrations of nicotine from 0.6 to 6.9 ug/m³. The authors concluded that because of the marked variability in measures, multiple measurements are needed to establish a stable profile of ETS exposure in the home environment.

To date, it would appear that there is only one large scale study in which homes have been *randomly* selected from the community at large for an ETS exposure assessment. This study is unique in that in that sampling took place over a 5 day period and measurement stability was assessed by repeat measurements one year after the initial sampling^{xxv}. The design and results from this investigation are reported in the next section⁽⁶⁾.

Measures of ETS Exposure in Random Sample of Canadian Homes

Study Design and Sample Selection

The sample selection process utilized census tracts for the city of Waterloo which has a population of about 80,000 and is located in the province of Ontario in Canada. The information obtained from the census was used to identify residential neighbourhoods in which the homes could be categorized as being “small-old”, “large-old”, “small-new”, and “large-new”. The actual age and size of the home was confirmed as part of the survey. Letters were sent to potential participants and then telephone calls made to determine eligibility and invite participation. The goal was to obtain approximately 200 households spread equally over the 4 categories.

As anticipated, the pool of potential participants decreased considerably at each stage of the recruiting process. A total of four thousand and thirty-eight letters were sent. Eighty-seven percent of the homes to which letters were sent were contacted. Fifty-one percent of these homes were eligible to participate in the study but only ten percent of the homes which met the eligibility criteria actually participated. The recruitment rates were similar for all four household types ranging from a low of 9% for the “small-old” category to a high of 11% for “small-new” homes.

The final sample set consisted of 48 homes in the “small-old” category with a median floor area of about 1000 sq. feet, 45 “large-old” homes with median floor area of about 1500 square feet, 59 “small-new”, homes with a median floor area of about 1300 square feet and 39 “large-new” homes with a median floor area of 2300 square feet. The median age of the “old” homes was approximately 40 years while the median age of the “new” homes was about 20 years. With respect to smoking habits, there were three types of participating households 137 homes in which there was at least one smoker and one non smoker 33 homes with smokers only and 21 homes in which all of the residents were non smokers and used as “negative” controls.

In the first category, that is smokers living with non smokers, the average number of cigarettes smoked per day was 18. In homes with just smokers the average cigarette consumption was 37 cigarettes per day about half of which were smoked in the home.

Households were visited twice. At the first visit, a questionnaire was used to obtain information about the household including the type of heating, use of fireplaces, humidifiers, solvents, and air cleaners. A second questionnaire was used to obtain demographic information, to determine behavioral characteristics relating to smoking and to assess attitudes towards ETS. At the end of the first visit, passive and active monitors were placed in the area with the greatest activity which was invariably the “living” or recreational room. The active monitor consisted of an SKC PCX-R7 personal monitoring pump programmed to sample intermittently at 1.5 litres per minute for 2700 minutes spread evenly over 5 day period which included the weekend. The pump was attached to a 3-way stream splitter which allowed samples to be collected for UVPM, solanesol, nicotine, 3 vinyl pyridine and carbonyls. A passive monitor was also used to obtain a second independent estimate for concentrations of nicotine.

At the second visit, an endpoint questionnaire was administered, a saliva sample collected and the monitors recovered. Filters and tubes were then labeled, returned to the laboratory and the cycle repeated until all of the households had been visited. This took approximately 5 months from November 1993 until June 1994.

⁶ Presented, in part, at the 49th Tobacco Chemists' Research Conference September 24-27, Lexington Kentucky, 1995. This investigation consisted of two studies carried out in 1994 and 1995. Both were both funded by the Canadian Federal Government through contracts to Labstat Incorporated. Principal investigators included Steve Brown and Rosemary Walker from the University of Waterloo, and Murray Kaiserman from Health Canada.

Results (Visit One)

Figure 7 illustrates the results for levels ETS surrogates broken down by smoking category. As shown here, there was a significant dependence of levels of tobacco smoke related particulates on level of smoking as one would expect. The concentration was virtually zero in non smoking homes rising to an average of about 32 ug/m^3 in homes in which there were smokers only⁷). The data for nicotine (active monitoring) and solanesol showed the same sort of dependency. The results for crotonaldehyde were both unexpected and interesting. The concentration of this compound was strongly related to the level of smoking which was not the case with any of the other carbonyls including formaldehyde and acetaldehyde. This suggests that crotonaldehyde could be another useful surrogate for ETS.

Another unexpected finding concerned concentrations of cotinine in saliva obtained from non smokers living with smokers. These were not related to levels of any of the ETS surrogates determined in the home (Figure 8). There are a number of explanations possible for the absence of a correlation but the fact that the home is only one of a number of sources of nicotine exposure ranks high on the list.

When the nicotine results from passive and active monitoring were compared, the hypothesis that the slope parameter was equal to one was accepted indicating agreement between the two measures (Figure 9). However the intercept term was significant suggesting a background level equivalent to about 1 ug/m^3 of nicotine. This could have come from the cassettes themselves, or could have been introduced during the preparation of the bisulfite treated filters which are part of the monitors.

⁷ Note: Average cigarette consumption in the "SA" homes was 9 per day in the home but 18 per day in the "SO" homes

Methods and Results (Visit Two)⁽⁸⁾

The second part of the investigation took place a year later and was undertaken to determine the stability of levels of the various measures and to validate the questionnaire responses obtained a year earlier. This aspect of the study involved revisiting a subset of about 50 homes chosen from those which had participated in the original 1994 study.

A list of potential candidates was developed based on the following criteria. To be included, the home must have had smoker cohabiting with nonsmoker and the home categorized as either “small-old” or “large-new”. There was the additional requirement that a complete set of ambient air measurements were available from the earlier project. 24 small old homes and 23 large new ones met these criteria. Eligible households were sent a letter explaining the purpose of this phase of the investigation and told to expect a phone call with regard to their participation. Each was contacted and during the phone conversation, it was determined that the same participants were still living in the home and that their smoking status had not changed (that is, the smoker still smoked and the nonsmoker still did not). In summary, a total of 62 letters were mailed and 58 of households were contacted by phone. Forty-one agreed to participate which is about 70% of those who could be contacted in contrast to the acceptance rate of about 10% in the initial investigation. Once subjects have part of a study of this sort, it would appear that there is an excellent chance that they would be willing to participate again.

The degree of correlation between the first and second surveys was investigated for each of the ambient air measures using both Pearson and Spearman correlation coefficients. Spearman coefficients, which are based on ranks are not as sensitive to outlying values. As shown in Table 3, there was a significant association between the 1994 and 1995 readings for nicotine, formaldehyde, acrolein, and crotonaldehyde. With respect to acrolein and formaldehyde this association was not significant when assessed using ranks.

Table 3: Correlation Coefficients and Tests of the Hypothesis : Intercept(b_0)= 0 by Constituent.

Constituent	Pearson Correlation Coefficient	Spearman Correlation Coefficient	$H_0 b_0:=0$ (p-value)
<i>Nicotine (passive monitor)</i>	<i>0.85 *</i>	<i>0.90 *</i>	<i>0.65</i>
Nicotine (active monitor)	0.57 *	0.49 *	0.0034 *
3-Vinylpyridine	0.23	0.17	0.0024 *
Salivary Cotinine	0.0031	-0.037	0.010 *
Solanesol	0.12	0.026	0.0070 *
UV Absorbing Matter (UVPM)	0.096	0.22	0.040 *
<i>Formaldehyde</i>	<i>0.36 *</i>	<i>0.29</i>	<i>0.47</i>
<i>Acetaldehyde</i>	<i>0.23</i>	<i>0.11</i>	<i>0.066</i>
Acetone	-0.067	-0.13	0.019 *
Acrolein	0.61 *	0.29	0.022 *
<i>Propionaldehyde</i>	<i>0.0087</i>	<i>-0.11</i>	<i>0.065</i>
<i>Crotonaldehyde</i>	<i>0.38 *</i>	<i>0.35 *</i>	<i>0.068</i>
Methyl Ethyl Ketone	0.067	0.055	0.019 *
<i>Butylaldehyde</i>	<i>0.21</i>	<i>0.17</i>	<i>0.11</i>
Total Carbonyls	-0.078	-0.013	0.043 *

* indicates significance at $\alpha = 0.05$

If the data from the two time periods agreed completely, a plot of the data should be linear with an intercept of zero and a slope of one. The hypothesis of a zero intercept was tested first since a “significant” intercept term would suggest that, on average, the 1995 readings were increased or decreased relative to those obtained in 1994. The p-values for these tests are shown in the last column in

⁸ When examining the, it is important to note that there was no evidence for a change in smoking rates during the interval between surveys. The correlation between the two occasions was 0.88 and is statistically significant ($p < .001$). The most notable change was in the non smokers self reported exposure to ETS. In 1994 35% of the subjects reported workplace exposure. In 1995 this decrease to 7%.

Table 4. Using a cut-off point of $p > .05$, there were six measure which, on average, had not changed between samplings.. Regression lines through the origin where then fit for this group and the resulting estimates for the slope parameter, are shown here. The hypothesis that the slope was equal to unity was tested and accepted for all of the compounds listed with the exception of butylaldehyde.

Table 4 : Tests of Hypothesis Beta = 1 for Constituents For Which the Intercept (b_0)= 0

MODEL: READING(1995) = b * (READING(1994))		
Constituent	Estimate for b	$H_0: b=1$ (p-value)
Nicotine (passive)	0.8727	0.1004
Formaldehyde	0.9341	0.5807
Acetaldehyde	1.344	0.0902
Proponaldehyde	1.190	0.4068
<i>Crotonaldehyde</i>	<i>0.9501</i>	<i>0.7271</i>
<i>Butylaldehyde</i>	<i>0.5192</i>	<i>0.0001 *</i>

** indicates significance at $\alpha = 0.05$*

Plots of the data are far more informative than estimates of regression coefficients. As shown in Figure 10, the stability of the nicotine results over time as determined by passive monitor, was quite remarkable. One might have anticipated that with the increased restrictions on smoking in public places in Ontario, including the work environment, there would have been more smoking in the home environment. This very limited data set does not support that particular suggestion.

Again, it was interesting to note that, levels of crotonaldehyde were also rather stable over the two sampling periods. This was encouraging with respect to the potential usefulness of this compound as a surrogate for ETS.

Summary

In summary, levels of ETS related constituents in a sample of Canadian homes are similar to those found in other investigations of the home environment. Concentrations were rather small, approaching analytical detection limits in some instances, but with remarkable stability over time particularly with respect to passive monitor nicotine and crotonaldehyde

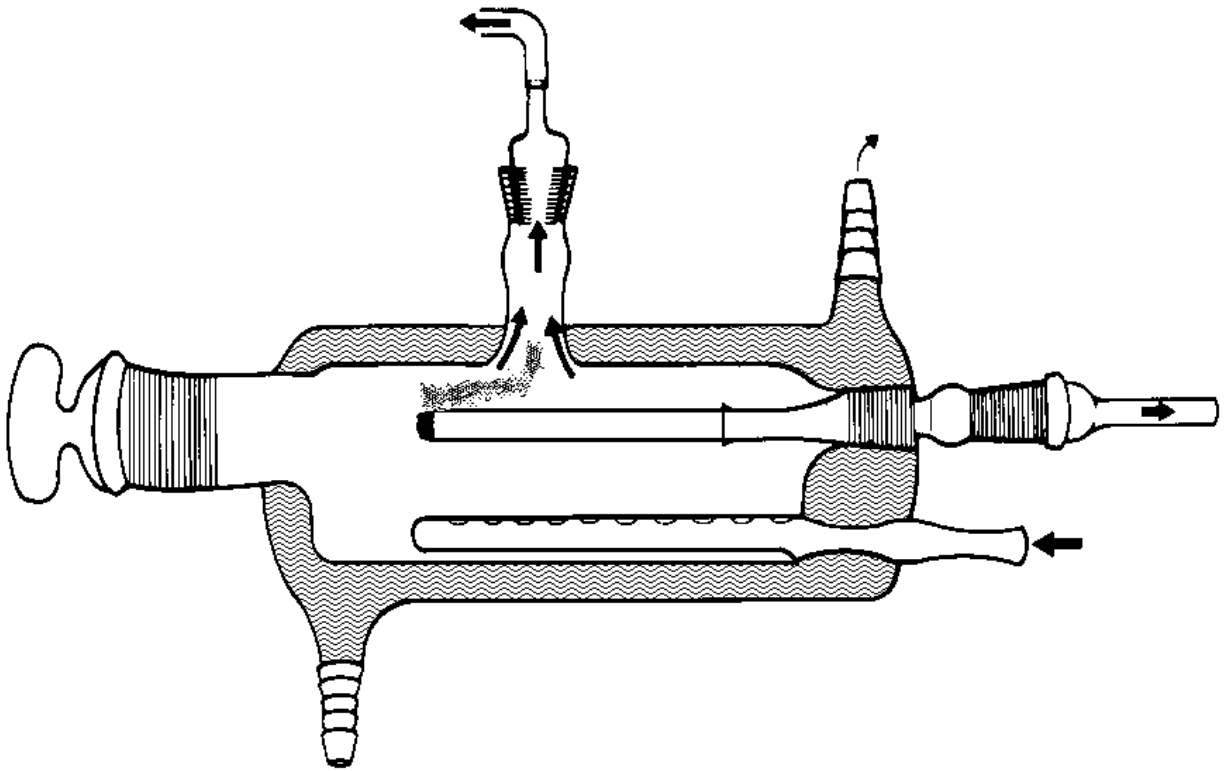


FIGURE 1

A. BAT Fish-tail Chamber (Diagram)

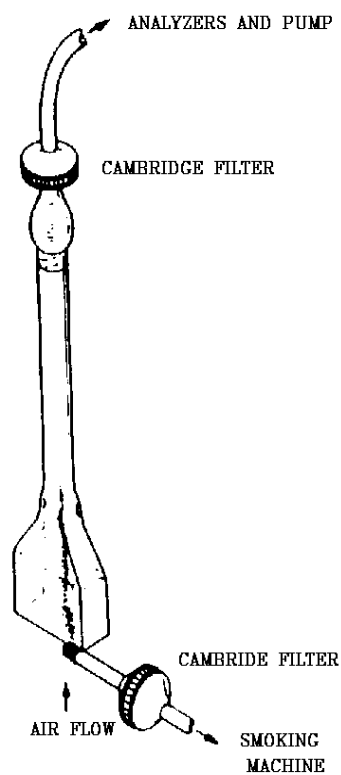
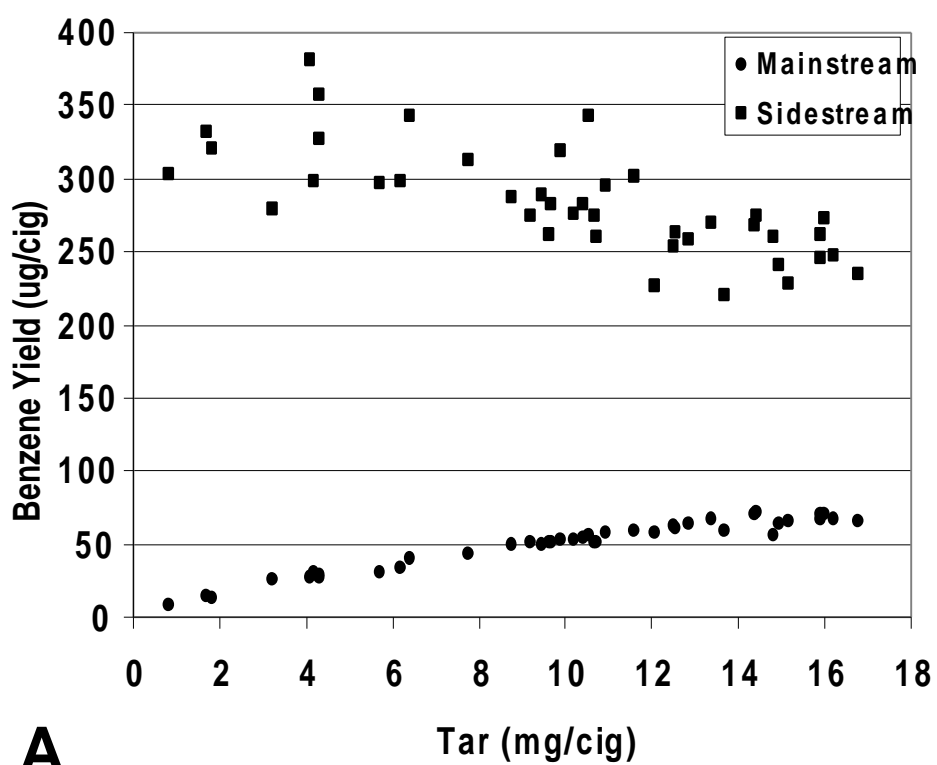


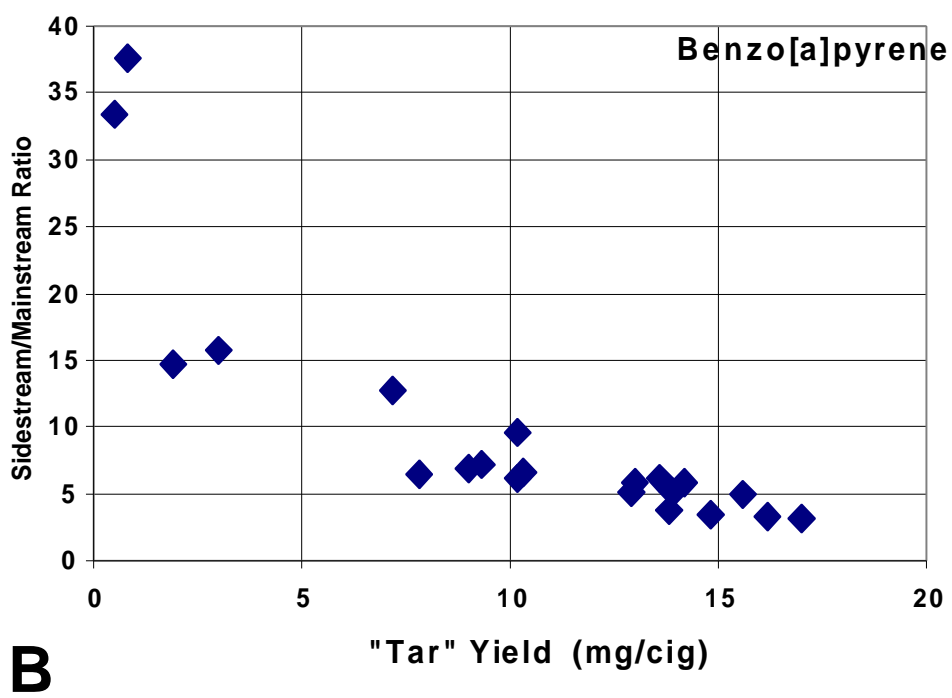
FIGURE 2

B. BAT Fish-tail Chamber (Example)



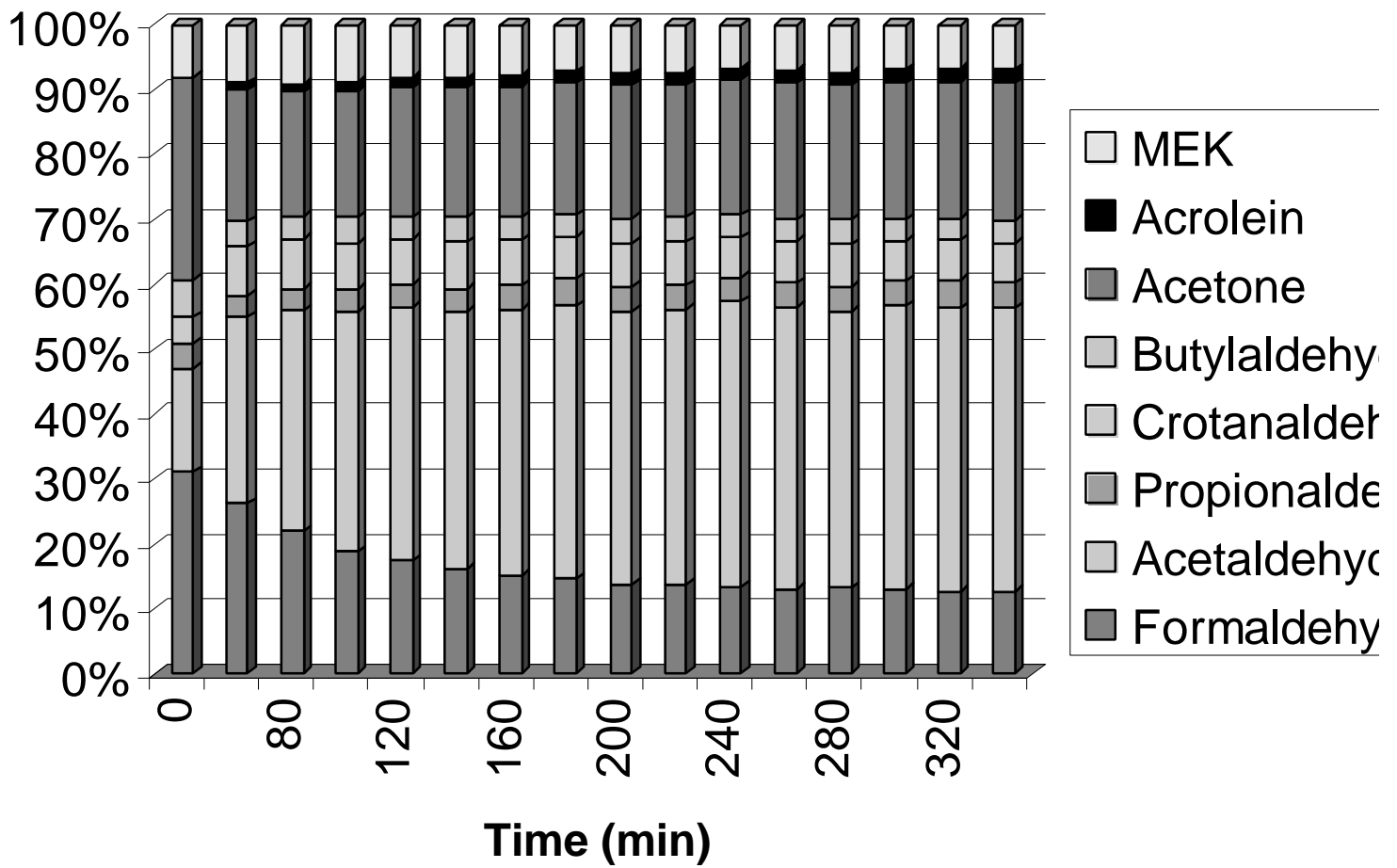


A



B

FIGURE 3



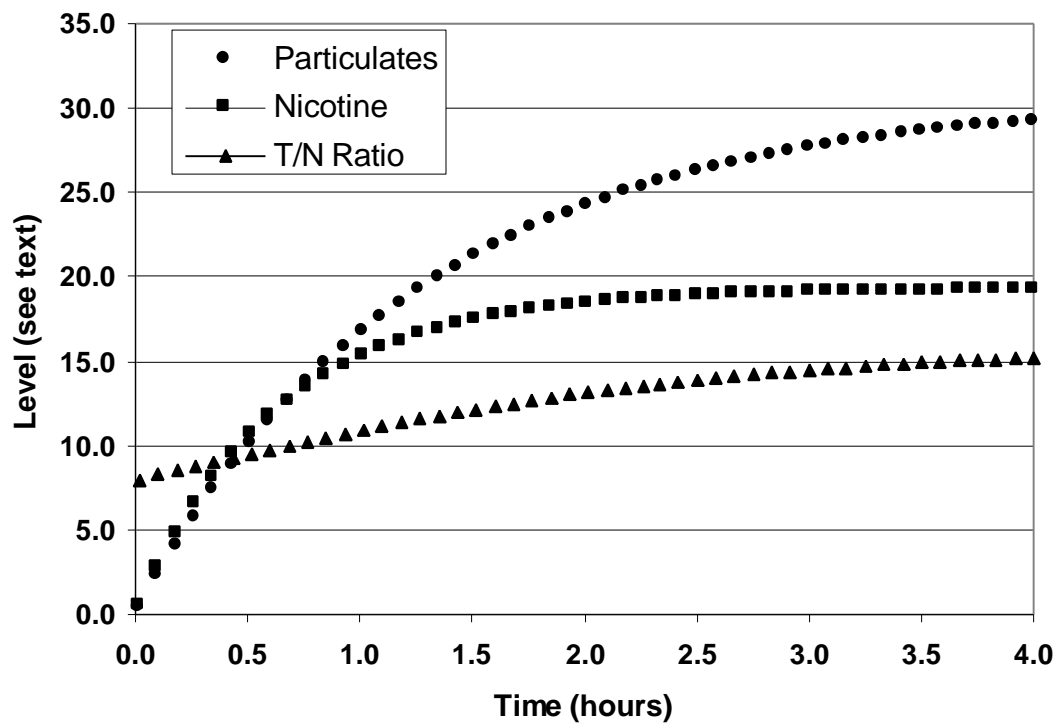
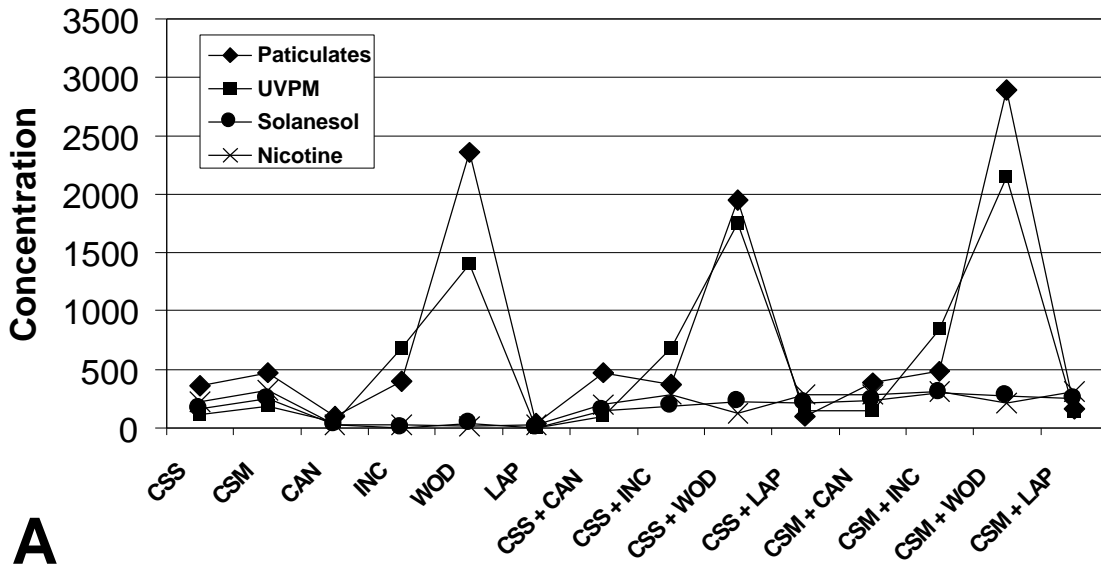
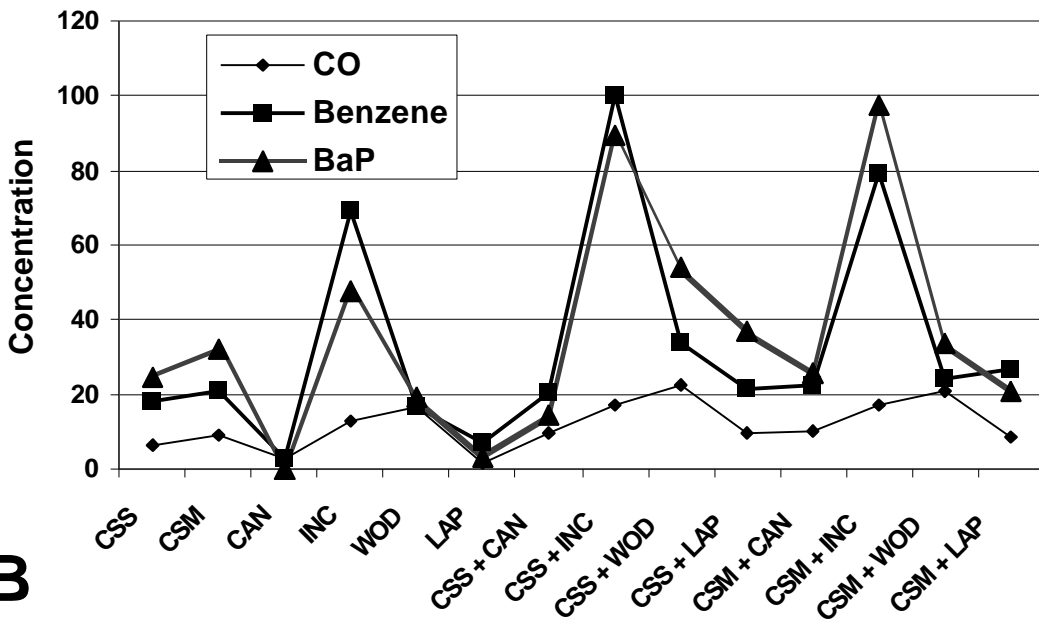


FIGURE 5

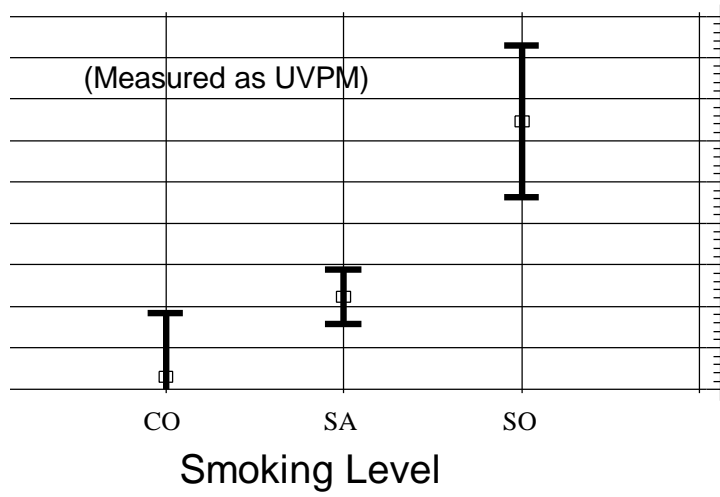


A

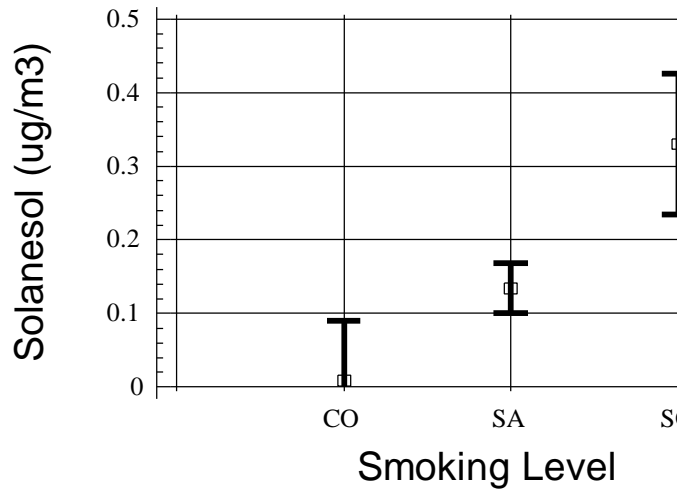


B

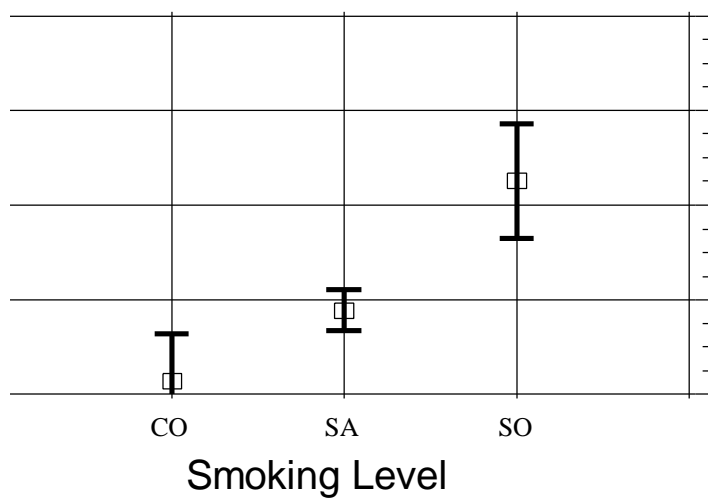
Smoke Particulates and Smoking Level



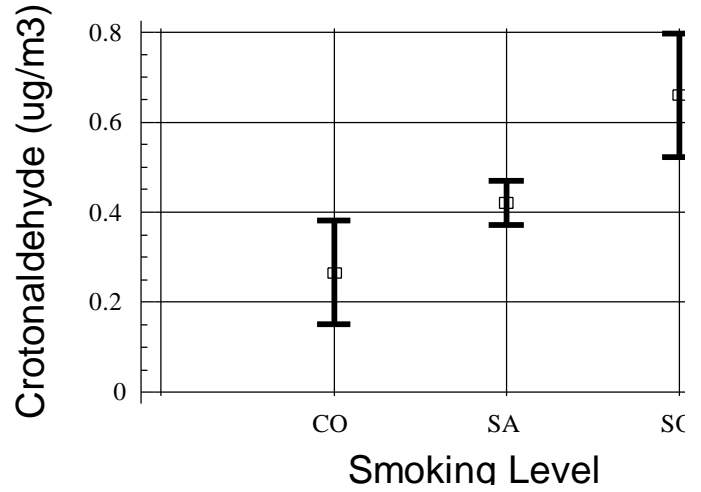
Solanesol and Smoking Level



Nicotine in Relation to Smoking Level



Crotonaldehyde and Smoking Level



Salivary Cotinine in Relation to Ambient Air Nicotine

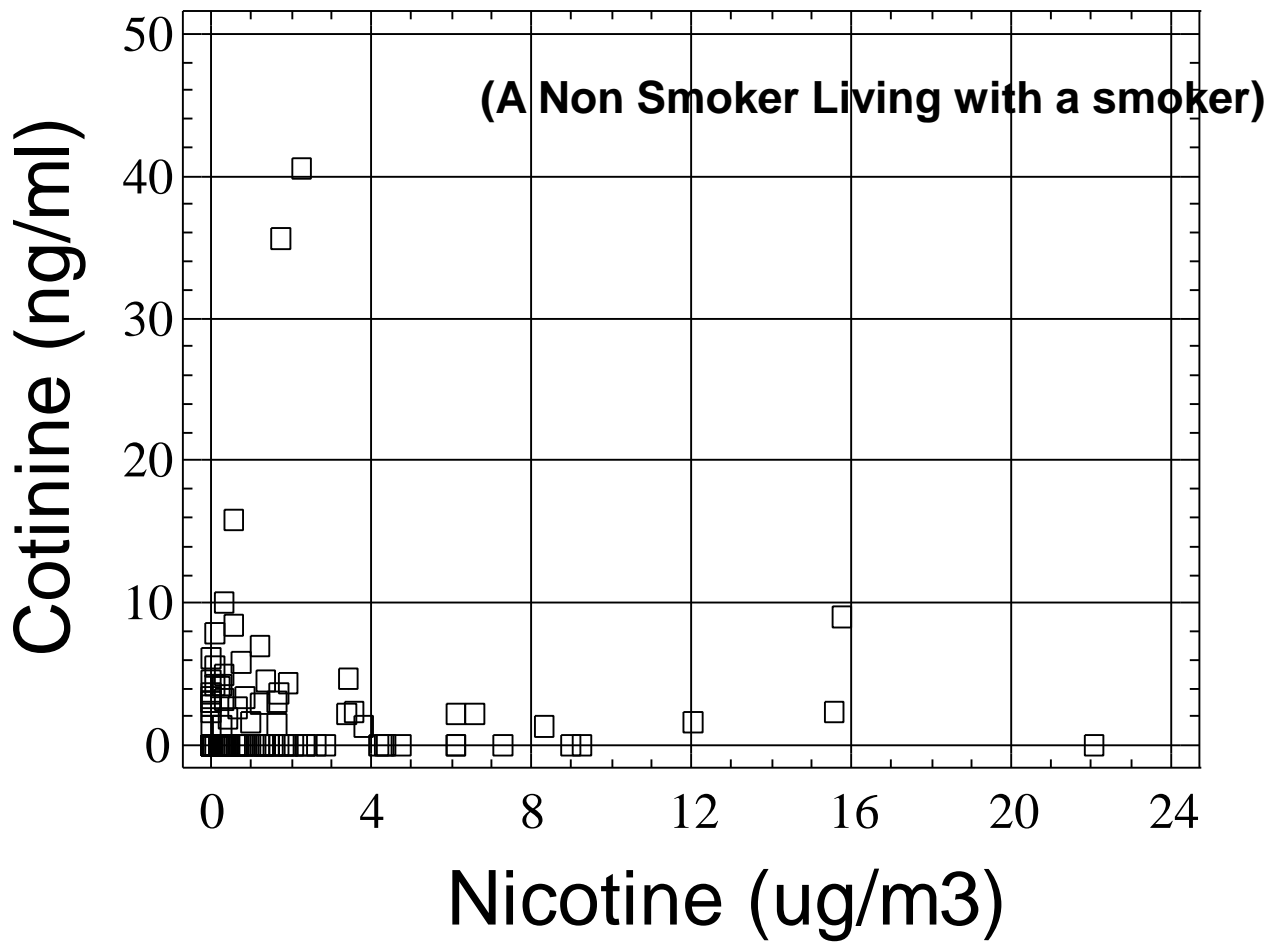


Figure 8

Figure 9

Figure 10

Legends for Figures

Figure 1: Modified Neurath chamber used in initial studies of the chemical composition of sidestream tobacco smoke (see reference 2 for further details).

Figure 2: Part A: A diagrammatic representation of a chamber for the collection of sidestream smoke first described in 1988 by a group of scientists working for the British American Tobacco Company (see reference 3 for further details). Part B. A photograph of sidestream chambers being used in smoke generation and collection.

Figure 3: Part A. Mainstream (MS) and sidestream(SS) yields of benzene in relation to mainstream yields of "tar". Results for 40 brands of Canadian cigarettes using a linear Filtrona 20 port linear smoking machine under 'standard' conditions (i.e. puff volume of 35 ml, 2 second duration with an interpuff interval of 58 seconds). Part B. SS:MS ratio in relation to MS "tar" for 20 brands of Canadian cigarettes.

Figure 4: Changes in the carbonyl composition of sidestream smoke with time. Sidestream tobacco smoke was generated continuously the sequential smoking of single cigarettes in a 27m³ controlled environment room (see text for further details)

Figure 5: Simulation of the changes in the concentration of nicotine ETS particulates and the particulate:nicotine ratio. Modeling involved the following assumptions: total volume of space, 340m³; single source of smoke (the equivalent of one cigarette burning continuously) and effective ventilation rate of 0.75 ACH. (See references 8-10 and text for further details)

Figure 6: Contribution of various common domestic sources of air pollution to levels of specific ambient air contaminants. Particulate levels in relation to ETS surrogates (UVPM, solanesol, and nicotine) illustrates that UVPM will overestimate ETS particulates in the presence of wood smoke. (see text for further details)

Figure 7: Average ETS surrogate response in relation to level of smoking for a random sample of Canadian homes (Abbreviations: CO, control homes (i.e. no smoking); SA, one smoker living with non smokers; SO, homes in which all of the adults were smokers).

Figure 8: Levels of salivary cotinine in relation to the concentration of nicotine in ambient air.

Figure 9: A comparison of results for ambient air nicotine obtained by two sampling methods

Figure 10: A comparison of levels of nicotine and crotonaldehyde in the same homes at two points in time separated by approximately one year.

References

- ⁱ Baker, R.R., and Proctor, C.J., The Origins and Properties of Environmental Tobacco Smoke. *Environ. Internatl.* 1990; 16:231-245
- ⁱⁱ Neurath, G., and Ehmke, H. Apparatur zur Untersuchung des Nebenstromrauches. *Beitr. Tabakforsch.* 1964; 2:117-121
- ⁱⁱⁱ Proctor, C.J., Martin, J.C., Beven, J.L., and Dymond, H.F., Evaluation of an Apparatus Designed for the Collection of Sidestream Tobacco Smoke. *Analyst.* 1988; 113:1509-1513
- ^{iv} Brunnemann, K.D., Kagan, M.R., Cox, J.E., and Hoffmann, D., Analysis of 1,3 butadiene and other selected gas-phase components in cigarette mainstream and sidestream smoke by gas chromatography-mass selective detection. *Carcinogenesis* 1990; 11:1863-1868
- ^v Bill C-71, An Act to Regulate the manufacture, sale, labeling and promotion of tobacco products, to make consequential amendments to another Act and to repeal certain Acts. Second Session, Thirty-fifth Parliament, 45-46 Elizabeth, II, 1996-1997. *Statutes of Canada* 1997, Chapter 13, Assented to 25th April 1997. Proposed Regulations: Information Letter dated June 10, 1998. I.L. No 819.
- ^{vi} Tobacco Control. A Blueprint to Protect the Health of Canadians. Published by the authority of the Minister of National Health and Welfare. ©Minister of Supply and Services Canada, 1995. Cat. H49-100/1995, ISBN 0-662-62149-2.
- ^{vii} Chemical and Biological Studies: New Cigarette Prototypes That Heat Instead of Burn Tobacco R.J. Reynolds Tobacco Company Winston-Salem, North Carolina (1988)
- ^{viii} Rickert, W.S., Robinson, J.C., and Collishaw, N. Yields of Tar, Nicotine and Carbon Monoxide in the Sidestream Smoke from 15 Brands of Canadian Cigarettes. *Am. J. Pub. Health* 1984; 74:228-231
- ^{ix} Deluca, P., Collection of Carbonyl Compounds in Environmental Tobacco Smoke Using 2,4-dinitrophenylhydrazine Coated Sep-pak Cartridges. 42nd Tobacco Chemists Research Conference, Lexington, Kentucky, October 2 – 5, 1988
- ^x Rickert, W.S., Some Consideration when Estimating Exposure to Environmental Tobacco Smoke [ETS] with Particular References to the Home Environment; *Can. J. Pub. Health* 1988; 79: S33-39.
- ^{xi} Repace, J.L. In *Environmental Carcinogens: Selected Methods of Analysis. Volume 9 Passive Smoking.* International Agency for Research on Cancer (IARC) Monograph on Sidestream Smoke 1987.
- ^{xii} Rickert, W.S., Robinson, J.C., and Collishaw, N.E., A Study of the Growth and Decay of Cigarette Smoke NO_x in Ambient Air Under Controlled Conditions. *Environ. Internatl.* 1987; 13:399-408.
- ^{xiii} Coghlin, J., Hammond, K.S., and Gann, P.H. Development of Epidemiologic Tools for Measuring Environmental Tobacco Smoke Exposure. 1989; *Am. J. Epiderm.* 130, 696-704.
- ^{xiv} Ogden, M.W., Heavner, D.L., Foster, T.L., Maiolo, K.C., Cash, S.L., Richardson, J.D., Martin, P., Simmons, P.S., Conrad, F.W., and Nelson, P.R. Personal Monitoring System for Measuring Environmental Tobacco Smoke Exposure. *Environ. Tech.* 1996; 17:239-250.
- ^{xv} Hammond, S.K., and Leaderer, B.P., A Diffusion Monitor to Measure Exposure to Passive Smoking. *Environ. Sci., Technol.* 1987; 21:494-497
- ^{xvi} Jaakkola, M.S., and Jaakkola, J.J.K., Assessment of Exposure to Environmental Tobacco Smoke. *Eur. Respir. J.* 1997; 10:2384-2397
- ^{xvii} EPA (Environmental Protection Agency). *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders.* EPA/600/6-90/006F. Washington, DC; December 1992. Available from: National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161. Order No. PB90-261-652/AS.

-
- ^{xviii} International Agency for Research on Cancer (IARC). Scientific Publications No 81. Environmental Carcinogens: Methods of Analysis and Exposure Measurement. Volume 9 Passive Smoking Editors I.K. O'Neill, K.D., Brunneman, B., Dodet, and Hoffman, D. (1987).
- ^{xix} NRC (National Research Council). Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects. Washington, DC: National Academy Press; (1986).
- ^{xx} Guerin, M.R., Jenkins, R.A., and Tomkins, B.A., The Chemistry of Environmental Tobacco Smoke: Composition and Measurement. Indoor air Research Series. M. Eisenberg editor, Lewis Publishers Inc. (1992)
- ^{xxi} Jenkins, R.A., Palausky, A., Counts, R.W., Bayne, C.K., Dindal, A.B., and Guerin, M.R. Exposure to Environmental Tobacco Smoke in Sixteen Cities in the United States as Determined by Personal Breathing Zone Sampling. *J. Exp. Anal. Environ. Epidemiol.* 1996; 6:473-502
- ^{xxii} Philips, K., Bentley, M.C., and Howard, D.A., Assessment of Air Quality in Paris by Personal Monitoring of Nonsmokers for Respirable Suspended Particles and Environmental Tobacco Smoke. *Environ. Internatl.* 1998; 405-425
- ^{xxiii} Ingebretsen, B.J., Heavner, D.L., Angel, A.L., Conner, J.M., Steichen, T.J., and Green, C.R. A Comparative Study of Environmental Tobacco Smoke - Particulate Mass in an Environmental Chamber. 1988; *JAPCA* 38, 413-417
- ^{xxiv} Standard Test Methods for Estimating Contribution of Environmental Tobacco Smoke to Respirable Suspended Particles Based on UVPM and FPM. ASTM Designation D 5955-96,
- ^{xxv} Conner, J.M., Oldaker III, G.B., and Murphy, J.J. Method for Assessing the Contribution of Environmental Tobacco Smoke to Respirable Suspended Particles in Indoor Environments. *Environ. Toxicol.* 1990; 11, 189-196
- ^{xxvi} Conner, J.M., Oldaker III, G.B., and Murphy, J.J. Method for Assessing the Contribution of Environmental Tobacco Smoke to Respirable Suspended Particles in Indoor Environments. *Environ. Toxicol.* 1990; 11, 189-196.
- ^{xxvii} Ogden, M.W., and Maioio, K.C. Collection and Determination of Solanesol as a Tracer of Environmental Tobacco Smoke in Indoor Air. *Environ. Sci. Technol.* 1989; 23, 1148-1154.
- ^{xxviii} Proctor, C.J., Warren, N.D., and Bevan, M.A.J. Measurements of Environmental Tobacco Smoke in an Air Conditioned Office Building, *Environ. Technol. Let.* 1989; 10, 1003-1018.
- ^{xxix} Henderson, F.W., Reid, H.F., Morris, R., Wang, O., Hu, P.C., Helms, R.W., Forehand, L., Mumford, J., Lewtas, J., Haley, N.J., and Hammond, S.K. Home Air Nicotine Levels and Urinary Cotinine Excretion in Preschool children. *Am. Rev. Respir. Dis.* 1989; 140; 197-201.
- ^{xxx} Standard Test Method for Nicotine in Indoor Air. ASTM Designation: D 5075-90a.
- ^{xxxi} Eatough, D.J., Benner, C.L., Tang, H., Landon, V., Richards, G., Caka, F.M., Crawford, J., Lewis, E.A., and Hansen, L.D., The Chemical Composition of Environmental Tobacco Smoke III. Identification of Conservative Tracers of Environmental Tobacco Smoke. *Environ. International.* 1989; 15: 19-28.
- ^{xxxii} McCarthy, J., Spengler, J., Chang, B.H., Coultas, D., Samet, J.A. A Personal Monitoring Study to Assess Exposure to Environmental Tobacco Smoke. Seifert, B., Esdorn, H., Fischer, M., Ruden, H., Wejner, J., eds. Proceedings, 4th International Conference on Indoor Air Quality and Climate. Berlin, Institute for Water, Soil and Air Hygiene. 1987; 2:142-146
- ^{xxxiii} Hammond, S.K., Coghlin, J. Field Study of Passive Smoking Exposure with Passive Sampler. Seifert, B., Esdorn, H., Fischer, M., Ruden, H., Wejner, J., eds. Proceedings, 4th international Conference on Indoor Air Quality and Climate. Berlin, Institute for Water, Soil and Air Hygiene. 1987; 2:131-136.
- ^{xxxiv} Eudy, L., Heavner, D., Stancill, M., Simmons, J.S., McConnell, B.): Measurement of Selected Constituents of Environmental Tobacco Smoke in a Winston-Salem, North Carolina Restaurant. Seifert, B., Esdorn, H., Fischer, M., Ruden, H., Wejner, J., eds. Proceedings, 4th International Conference on Indoor Air Quality and Climate. Berlin, Institute for Water, Soil and Air Hygiene. 1987; 2:126-130
- ^{xxxv} Tang, H., Richard, G., Gunther, K., Crawford, J., Lee, M.L., Lewis, E.A., and Eatough, D.J. Determination of Gas Phase Nicotine and 3-ethylpyridine and Particulate Phase Nicotine in Environmental Tobacco Smoke with a Collection Bed-Capillary Gas Chromatography System. *J.*

High. Res. Chromatog. Chromatog. Commun. 1988; 11:775-782.

^{xxxvi} Standard Test Method for Nicotine and 3-Ethenylpyridine in Indoor Air. ASTM Designation D 5075-96

^{xxxvii} Ogden, M.W. and Maioio, K.C.: Gas Chromatographic Determination of Solanesol in Environmental Tobacco Smoke (ETS) *J. High Resolut. Chromatogr., Chromatogr. Commun.* (1988; II:341-343).

^{xxxviii} Ogden, M.W., and Maioio, K.C. Collection and Determination of Solanesol as a Tracer of Environmental Tobacco Smoke in Indoor Air. *Environ. Sci. Technol.*(1989;: 23:1148-1154.

^{xxxix} Ogden, M.W., and Maioio, K.C.: Comparison of GC and LC for Determining Solanesol in Environmental Tobacco Smoke. *LC.GC.* 1992; 10:459-462.

^{xl} Nelson, P.R., Conrad, F.W., Kelly, S.P., Maiolo, K.C., Richardson, J.D., and Ogden, M.W. Composition of Environmental Tobacco Smoke (ETS) from International Cigarettes and Determination of ETS-RSP Particulate Marker Ratios. *Environ. Internatl.* 1997; 23:47-52

^{xli} S. Matsushima and S. Sugawara. Composition studies on some varieties of tobacco and their smoke (III). Hydrophobic solvent extracts of tobacco leaves. *Kenkyu Hokoku Nippon Senbai Kosha Chuo Kenkyusho.* 1983; 125: 17-24.

^{xlii} Risner, C.H., and Nelson, P.R., Determination of (+)-a-Tochopherol in Environmental Tobacco Smoke *J. Chromatog. Sci.* 1998; 36:80-84

^{xliii} Rickert, W.S., Robinson, J.C., and Kaiserman, M.J. Quantitation of "Tar" Colour with Specific Reference to Estimating Yields, Quantifying ETS and the Production of Colour Scales. 48th Tobacco Chemists' Research Conference, Greensboro, North Carolina, 1994.

^{xliv} Byrd, G.D., Robinson, J.H., Caldwell, W.S., and deBethizy, J.D., Nicotine Uptake and Metabolism in Smokers. *Rec. Adv. Tob. Sci.* 1994; 20:5-31

^{xlv} Jarvis MJ, Russell MAH, Feyerabend C. "Absorption of Nicotine and Carbon Monoxide from Passive Smoking Under Natural Conditions of Exposure." *Thorax*, 1983; 38:829-833

^{xlvi} Jarvis MJ, Russell MAH, Feyerabend C, Eiser JR, Morgan M, Gammage P, Gray EM. "Passive Exposure to Tobacco Smoke: Saliva Cotinine Concentrations in a Representative Population Sample of Nonsmoking Schoolchildren." *Br Med J*, 1985; 291:927-9

^{xlvii} Scherer G, Conze CH, v.Meyerinck L, Sorsa M, Adlkofer F. "Importance of Exposure to Gaseous and Particulate Phase Components of Tobacco Smoke in Active and Passive Smokers." *Int Arch Occup Environ Health*, 1990; 62:459-66.

^{xlviii} . Scherer G, Westphal K, Adlkofer F. "Urinary Mutagenicity, Hydroxphenanthrene, and Thioether Excretion After Exposure to Environmental Tobacco Smoke." In: *Indoor Air Quality.* Kasunga H ed Springer-Verlag Berlin Heidelberg, 1990; 138-146.

^{xlix} Scherer G, Conze C, Tricker AR, Adlkofer F. "Uptake of Tobacco Smoke Constituents on Exposure to Environmental Tobacco Smoke (ETS)." *Clin Invest*, 1992; 70:352-67

^l Neurath GB, Dunger M, Orth D, Pein FG. "Trans-3'-hydroxycotinine as a Main Metabolite in Urine of Smokers." *Int Arch Occup Environ Health*, 1987; 59:199-201

^{li} Neurath GB, Dunger M, Orth D, Pein FG. "Trans-3'-hydroxycotinine as a Main Metabolite in Urine of Smokers." *Int Arch Occup Environ Health*, 1987; 59:199-201

^{lii} Kyerematen GA, Morgan ML, Chattopadhyai B, deBethizy JD, Vesell ES. "Disposition of Nicotine and Eight Metabolites in Smokers and Nonsmokers: Identification in Smokers of Two Metabolites that Longer Lived Than Nicotine." *Clin Pharmacol Ther*, 1990; 48:641-51

^{liiii} . Jacob III P, Shulgin AT, Benowitz NL. "Synthesis of (3'R,5'S)-trans-3'-hydroxycotinine, a Major Metabolite of Nicotine. Metabolic Formation of 3'-hydroxycotinine in Humans is Highly Stereoselective." *J Med Chem*, 1990; 33:1888-1891

^{liv} Guerin MR, Jenkins RA, Tomkins BA. "The Chemistry of Environmental Tobacco Smoke: Composition and Measurement." *Ann Arbor, MI: Lewis Publishers; 1992*

^{lv} Rodgman A. "Environmental Tobacco Smoke." *Regulat Toxicol Pharmacol*, 1992; 16:223-44.

^{lvi} Roberfroid MB. Correlating Exposure to Environmental Tobacco Smoke Exposure with Increased Incidence of Lung Cancer in Nonsmokers: is Cotinine a Valid Marker? *The Cancer Journal*, 1994; 7(3):108-114

^{lvii} Benowitz, N.L., Cotinine as a Biomarker of Environmental Tobacco Smoke Exposure.

-
- Epidem. Rev. 1996; 18:188-204.
- ^{lviii} Hoffmann, D., and Hoffmann, I., The Changing Cigarette, 1950 – 1995. *J. Toxicol. Environ. Health* 1997; 50:307-364
- ^{lix} Hecht, SS. Environmental Tobacco Smoke and Lung Cancer: the Emerging Role of Carcinogen Biomarkers and Molecular Epidemiology. *J Natl Cancer Inst*, 1994; 86(18):1369-70
- ^{lx} Crawford FG, Mayer J, Santella RM, et al. "Biomarkers of Environmental Tobacco Smoke in Preschool Children and their Mothers." *J Natl Cancer Inst*, 1994; 86:1398-1402
- ^{lxi} Bartsch H, Kadlubar F, O'Neill I eds. Biomarkers in Human Cancer - Part II - Exposure Monitoring and Molecular Dosimetry. *Environ Health Perspect*, Vol 99. DHHS Publ No. (NIH)93-218. Research Triangle Park, NC: NIEHS, 1993
- ^{lxii} Hulka BS. ASPO Distinguished Achievement Award Lecture. *Epidemiological Studies Using Biological Markers: Issues for Epidemiologists. Cancer Epidemiol Biomarkers prev*, 1991; 1:13-19
- ^{lxiii} Crawford FG, Mayer J, and Santella RM Biomarkers of Environmental Tobacco Smoke in Preschool Children and Their Mothers. *J Natl Cancer Inst*, 1994; 86:1398-1402.
- ^{lxiv} Skipper PL, Tannenbaum SR. Protein Adducts in the Molecular Dosimetry of Chemical Carcinogens *Carcinogenesis*, 1990; 11:507-518
- ^{lxv} Lee BM, Santella RM. Quantitation of Protein Adducts as a Marker of Genotoxic Exposure: Immunologic Detection of Benzo(a)pyreneglobin adducts in mice. *Carcinogenesis*, 1988; 9:1773-1777
- ^{lxvi} Shugart L, Kao J. Examination of Adduct Formation in vivo in the Mouse between Benzo(a)pyrene and DNA of Skin and Hemoglobin of Red Blood Cells. *Environ Health Perspect*, 1985; 62:223-226
- ^{lxvii} Pereira MA, Lin L-HC, Chang LW. Dose-Dependency of 2-Acetylaminofluorene Binding to Liver DNA and Hemoglobin in Mice and rats. *Toxicol Appl Pharmacol*, 1981; 60:472-478.
- ^{lxviii} Marbury MC, Hammond SK, Haley NJ. Measuring Exposure to Environmental Tobacco Smoke in Studies of Acute Health Effects. *American Journal of Epidemiology*, 1993; 137(10):1089-97.
- ^{lix} Philips, K., Howard, D.A., Bentley, M.C. and Alvan, G., Assessment of Environmental Tobacco Smoke and Respirable Suspended Particle Exposures for Nonsmokers in Lisbon by Personal Monitoring. *Environ. Internatl.* 1998; 24:301-324.
- ^{lxx} Philips, K., Howard, D.A., Bentley, M.C., and Alvan, G., Assessment of Environmental Tobacco Smoke and Respirable Suspended Particle Exposures for Nonsmokers in Paris by Personal Monitoring. *Environ. Internatl.* 1998; 24:405-425.
- ^{lxxi} Philips, K., Howard, D.A., Bentley, M.C., and Alvan, G., Assessment of Environmental Tobacco Smoke and Respirable Suspended Particle Exposures for Nonsmokers in Turin by Personal Monitoring. *Environ. Internatl.* 1997; 23:851-871.
- ^{lxxii} Phillips, K., Howard, D.A., Bentley, M.C., and Alvan, G., Measured Exposures by Personal Monitoring for Respirable Suspended Particles and Environmental Tobacco Smoke of Housewives and Office Workers Resident in Bremen, Germany. *Int. Arch. Occup. Environ. Health.* 1998; 71:201-212
- ^{lxxiii} Ogden, M.W., and Martin, P., The Use of Cigarette Equivalents to Assess Environmental Tobacco Smoke Exposure. *Environ. Internatl.* 1997; 23:123-128
- ^{lxxiv} Coultas, D.B., Samet, J.M., McCarthy, J.F., and Spengler, J.D., Variability of Measures of Exposure to Environmental Tobacco Smoke in the Home. 1990; *Am. Rev. Respir. Dis.* 142:602-606
- ^{lxxv} Rickert, W.S., Brown, S.K., Walker, R., and Kaiserman, M.J., (1995) Levels of ETS Particulates, Nicotine Solanesol, and Carbonyls in a "Random" Selection of Homes in a Midsized Canadian City. 49th Tobacco Chemists' Research Conference Lexington Kentucky, September 24-27, 1995.